Comparing aliphatic nitriles to potassium cyanide using EEG based methods

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Introduction

Aliphatic nitriles are a group of organic compounds characterized by a carbon–nitrogen triple bond (C≡N) and the general formula R–CN. They are widely used in the synthesis of plastics, fibers, resins, dyes, and pharmaceuticals. Although essential to manufacturing and research, many are recognized as highly hazardous due to their acute toxicity and risk of accidental exposure.

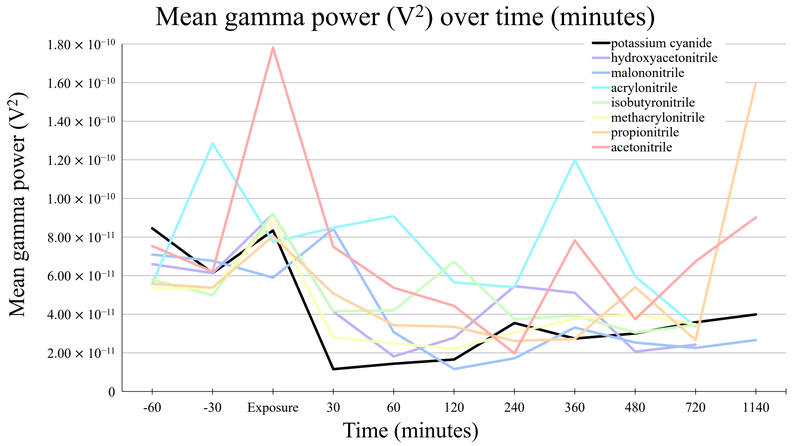
Historically, research on nitrile toxicity has focused on nitrile ability to release cyanide during metabolism. Willhite and Smith (1981) demonstrated that cyanide liberation is a key determinant of the acute toxicity of many aliphatic nitriles. However, their study also noted that some nitriles produce toxic effects not fully explained by cyanide formation alone, suggesting additional metabolic or parent compound specific mechanisms.

In the present study, electroencephalogram (EEG) recordings of delta and gamma waves were used to monitor changes in brain activity following subcutaneous administration of several aliphatic nitrile compounds. Delta waves are slow, high amplitude, oscillations, associated with deep sleep, reduced consciousness, or brain injury; while gamma waves are fast, low amplitude, oscillations, linked to higher cognitive functions such as attention, sensory integration, and working memory. By analyzing mean voltage squared values over time, this experiment aimed to determine how different nitriles affect brain function and whether toxicity correlates with specific patterns of neural disruption. The purpose of this study was to see how the EEG recordings from rats exposed to nitriles were compared to those exposed to potassium cyanide.

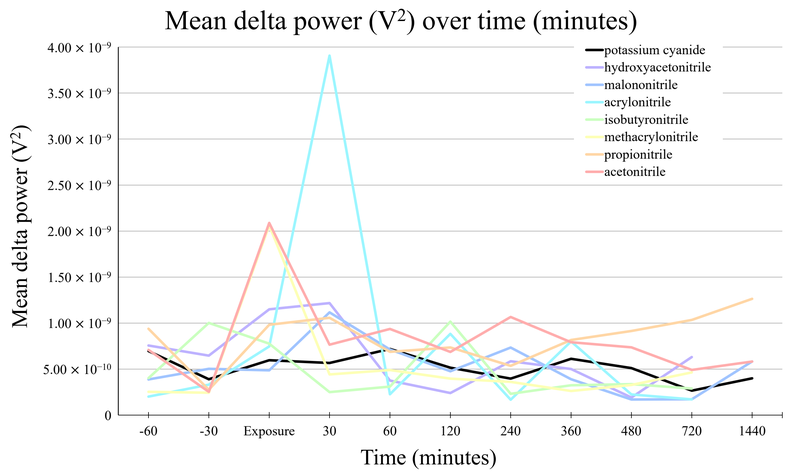
Methods and Materials

This study used Sprague Dawley rats, selected for their consistent responses in toxicology research. The chemicals tested included potassium cyanide, hydroxyacetonitrile, acrylonitrile, malononitrile, isobutyronitrile, propionitrile, acetonitrile, and methacrylonitrile. The sample consists of two groups of eight rats per chemical, for a total *n* of 128. On experiment day, baseline EEG recordings were taken for one hour, followed by subcutaneous injection of the chemical of interest. Post exposure monitoring and EEG recordings occurred from 0 to 24 hours, with extended observation from days 1 to 10 before study completion. Recordings were segmented into ten-minute intervals, and mean voltage squared was calculated for each rat. Values were organized and compared across chemicals and time points.

Results



Graph 1 (above): A mixed effects model was used to examine the effects of chemical type and timepoint on gamma power, with cage included as a random effect. There were significant main effects of chemical, $F(7, 1086.28) = 6.02$, $p < .001$, and timepoint, $F(9, 1080.42) = 8.76$, $p < .001$. The chemical × timepoint interaction was not significant, $F(63, 1080.25) = 1.25$, $p = .094$. Gamma power peaks at exposure and is reduced across multiple post exposure intervals, indicating a sustained decrease over time. Because mortality was not evenly distributed across chemicals, estimates at later timepoints should be interpreted with caution.



Graph 2 (above): A mixed effects model was used to examine the effects of chemical type and timepoint on delta power, with cage included as a random effect. Timepoint significantly affected power, $F(9, 1099.01) = 3.90$, $p < .001$, while chemical did not, $F(7, 1103.67) = 1.34$, $p = .228$; however, the chemical × timepoint interaction was significant, $F(63, 1098.98) = 1.46$, $p = .013$. Variability between compounds increased at later timepoints due to differential mortality.

Results (cont.)

Gamma						Delta				
Chemical	Mean (V^2)	Grouping				Chemical	Mean (V^2)	Grouping		
acrylonitrile	7.61×10^{-11}	A				acetonitrile	8.43×10^{-10}	A		
acetonitrile	6.90×10^{-11}	A	B			propionitrile	8.35×10^{-10}	A		
isobutyronitrile	4.91×10^{-11}		B	C		acrylonitrile	7.72×10^{-10}	A		
propionitrile	4.70×10^{-11}		B	C		hydroxyacetonitrile	6.31×10^{-10}	A		
hydroxyacetonitrile	4.58×10^{-11}		B	C		potassium cyanide	5.27×10^{-10}	A		
malononitrile	4.24×10^{-11}			C		methacrylonitrile	5.20×10^{-10}	A		
methacrylonitrile	4.07×10^{-11}			C		malononitrile	5.18×10^{-10}	A		
potassium cyanide	4.00×10^{-11}			C		isobutyronitrile	5.11×10^{-10}	A		
Gamma						**Delta**				
Timepoint (minutes)	Mean (V^2)	Grouping				Timepoint (minutes)	Mean (V^2)	Grouping		
0	9.36×10^{-11}	A				30	1.20×10^{-9}	A		
−30	6.75×10^{-11}	A	B			0	1.12×10^{-9}	A	B	
−60	6.53×10^{-11}	A	B	C		120	6.17×10^{-10}	A	B	C
30	5.25×10^{-11}		B	C	D	60	5.65×10^{-10}	A	B	C
360	5.21×10^{-11}		B	C	D	360	5.62×10^{-10}		B	C
60	3.90×10^{-11}			C	D	−60	5.47×10^{-10}		B	C
480	3.76×10^{-11}			C	D	240	5.10×10^{-10}		B	C
720	3.52×10^{-11}				D	−30	4.55×10^{-10}			C
120	3.50×10^{-11}				D	720	4.40×10^{-10}			C
240	3.47×10^{-11}				D	480	4.27×10^{-10}			C

Table 1 (above): A visual representation of the Tukey-multiple comparisons test done after both mixed effects models. Means that do not share a letter are significantly different.

Discussion

The purpose of this study was to see how the EEG recordings from rats exposed to nitriles were compared to those exposed to potassium cyanide (KCN). Behavioral observations taken during post exposure monitoring provided insight into how the animals responded following exposure. Pathological data and other measurements recorded during the time of exposure were also considered when evaluating the overall toxicity of each compound. Based on these combined findings, hydroxyacetonitrile and malononitrile appeared to produce effects and signs of acute toxicity most like those observed with KCN and associated with cyanide exposure.

Overall, these results highlight the importance of further research on aliphatic nitriles and their neurological impacts. Continued investigation may contribute to the development of more effective treatments or antidotes and deepen the scientific understanding of aliphatic nitriles.

References

Willhite, C. C. & Smith, R. P. (1981). The role of cyanide liberation in the acute toxicity of aliphatic nitriles. *Toxicology and Applied Pharmacology*, *59*(3), 589–602. https://doi.org/10.1016/0041-008x(81)90314-8